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ARTICLE

Cost-effectiveness of Population Screening for BRCA Mutations in Ashkenazi Jewish Women Compared With Family History–Based Testing

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Abstract

Background: Population-based testing for BRCA1/2 mutations detects the high proportion of carriers not identified by cancer family history (FH)–based testing. We compared the cost-effectiveness of population-based BRCA testing with the standard FH-based approach in Ashkenazi Jewish (AJ) women.

Methods: A decision-analytic model was developed to compare lifetime costs and effects amongst AJ women in the UK of BRCA founder-mutation testing amongst: 1) all women in the population age 30 years or older and 2) just those with a strong FH (≥10% mutation risk). The model assumes that BRCA carriers are offered risk-reducing salpingo-oophorectomy and annual MRI/mammography screening or risk-reducing mastectomy. Model probabilities utilize the Genetic Cancer Prediction through Population Screening trial/published literature to estimate total costs, effects in terms of quality-adjusted life-years (QALYs), cancer incidence, incremental cost-effectiveness ratio (ICER), and population impact. Costs are reported at 2010 prices. Costs/outcomes were discounted at 3.5%. We used deterministic/probabilistic sensitivity analysis (PSA) to evaluate model uncertainty.

Results: Compared with FH-based testing, population-screening saved 0.090 more life-years and 0.101 more QALYs resulting in 33 days’ gain in life expectancy. Population screening was found to be cost saving with a baseline-discounted ICER of -£2079/QALY. Population-based screening lowered ovarian and breast cancer incidence by 0.34% and 0.62%. Assuming 71% testing uptake, this leads to 276 fewer ovarian and 508 fewer breast cancer cases. Overall, reduction in treatment costs led to a discounted cost savings of £3.7 million. Deterministic sensitivity analysis and 94% of simulations on PSA (threshold £20000) indicated that population screening is cost-effective, compared with current NHS policy.

Conclusion: Population-based screening for BRCA mutations is highly cost-effective compared with an FH-based approach in AJ women age 30 years and older.
Genetic testing for high-penetration BRCA mutations is currently restricted to individuals from high-risk families fulfilling stringent family history (FH)-based criteria. However, a large proportion of BRCA carriers do not fulfill the current threshold for genetic testing. We found that more than 50% of BRCA carriers are missed by the FH-based approach, which is consistent with some earlier reports in which 40% to 63% (1-3) of carriers in population cohorts and 50% to 75% of carriers from cancer case series unselected for FH (4-9) lacked a strong FH of cancer. New gene-sequencing technologies (10) and the falling cost of genetic testing will make it feasible to test large populations in the near future. This could lead to new approaches capable of detecting a larger proportion of carriers of high-penetration mutations and a change from the current FH-based approach. Systematic BRCA founder mutation (FM) testing in a low-risk Ashkenazi Jewish (AJ) population is acceptable and is not associated with differences in short-term psychological or quality-of-life outcomes compared with an FH-based approach (11). The AJ population could be the first population for whom population-based testing is feasible.

A health-economic evaluation is essential for an overall assessment of the balance of costs and health benefits in the context of setting public health policy for genetic testing of high-penetration cancer gene mutations. Decision-analytical modeling compares the expected costs and consequences of decision options by synthesizing information from multiple sources and applying mathematical techniques, usually with computer software (12). The current clinical approach, which uses high-risk families for case identification, is more cost-effective than no genetic screening with a cost-effectiveness ratio (CER) of 4294 euros per life-year-gained reported (13). In addition, preventive surgery is more cost-effective than screening in known BRCA and mismatch repair (MMR) gene carriers (14-16). However, health-economic data using truly population-based ascertainment are limited. There is only one cost-utility analysis comparing population-based screening with no screening in the AJ population (17), which found that screening would prevent 2811 ovarian cancers in the United States, for a (discounted) program cost of $8300 per quality-adjusted-life-year (QALY). However, to date, the cost-effectiveness of a population-based approach has not been compared with an FH-based approach. Genetic Cancer Prediction through Population Screening (GCaPPS) is a randomized trial (ISRCTN73338115) comparing outcomes of population and FH-based approaches for genetic testing in UK AJ women. In order to provide policy makers with the best available evidence, we use data from the GCaPPS trial to describe a decision analysis model comparing both population and FH-based approaches for genetic-testing in AJ women.

Methods

A decision analytic model (Figure 1) was developed to compare the lifetime costs and effects of genetically screening all UK AJ women age 30 years and older for BRCA FM, compared with the current practice of screening using FH-based criteria (≥10% mutation risk) (Supplementary Table 1, available online). The model assumes that all women in the population screening arm and only those with a strong FH in the FH arm are offered genetic counseling and genetic testing. A 71% uptake rate of genetic testing (estimated from the GCaPPS study) was incorporated into the model. Genetic testing involved analysis for the three BRCA FM associated with Jewish descent in a National Health Service (NHS) genetics laboratory. In line with current guidelines (18,19) women testing positive were offered risk-reducing salpingo-oophorectomy (RRSO) to reduce their ovarian cancer risk (20,21) and MRI/mammography screening or risk-reducing mastectomy (RRM) (22) to reduce their breast cancer risk. Use of a selective estrogen receptor modulator (SERM) for breast cancer chemoprevention (23) was also included in the model as part of a sensitivity analysis, but ovarian cancer screening was excluded, as its clinical value remains uncertain (24). In line with guidelines on the reference case for economic evaluation from the National Institute of Health and Clinical Excellence (NICE), all costs and outcomes were discounted at 3.5% (25).

Probabilities

All pathway probabilities for the model are presented and explained in Table 1. A one-way sensitivity analysis involved rerunning the model at both lower and upper values/limits of the 95% confidence interval or range of all probability parameters (Table 1) used in the model (Figures 2 and 3). Cancer incidence was estimated by summing the probabilities of pathways ending in ovarian or breast cancer. The current estimated UK population of AJ women is 114400 (26,27). The total population impact was estimated by multiplying the results per woman by 81224 (0.71*114400). Additionally, the effect if all 114400 women underwent testing was also calculated.

Costs

All costs are reported at 2010 prices and where required have been converted using the Hospital and Community Health Service Index (28). These are described in detail in Table 2.

Life-years

Life expectancy for women not developing cancer (age 53 years) was based on life-tables from the Office of National Statistics (29). The mean age for breast/ovarian cancer onset was age 41.7/51.5 years for BRCA1 and 45.6/58.9 years for BRCA2 AJ women, respectively (30). To simplify the analysis, we used average ages for breast (43.5 years) and ovarian cancer (54.9 years) onset for BRCA1/BRCA2 carriers, obtained by assigning weights to the individual ages of onset for the relative population prevalence of BRCA1 and BRCA2 FM ((1.32*AgeBRCA1)/2.45 + (1.13*AgeBRCA2)/2.45). The mean ages for sporadic breast and ovarian cancer in AJ-women were 57 years and 63 years, respectively (31-33). In the absence of AJ-specific survival data, five-year survival rates were assumed to be the same as the general UK population (34). This model incorporates potential survival differences between BRCA1, BRCA2, and sporadic ovarian cancers (35,36). No statistically significant survival difference between BRCA and sporadic breast cancers has been reported (37,38). For ovarian cancer, the five-year survival for BRCA1 is 44% (95% confidence interval [CI] = 40% to 48%) and for BRCA2 52% (95% CI = 46% to 58%) (35), giving a composite five-year survival for BRCA1+BRCA2 (weighted by BRCA1 and BRCA2 prevalence) of 0.477 ((0.44*1.32/2.45)+(0.52*1.13/2.45)). After five years’ survival, the probability of death was assumed to be the same as the general population.

Quality-Adjusted Life-years (QALYs)

QALY is a measurement that expresses changes in length of life, while at the same time incorporating reductions in quality-of-life. Calculation of QALYs requires knowledge of quality-of-life adjustment or utility weights for each health state in the
model. Utility weights are an indication of an individual’s preference for specific health states where 1 equals perfect health and 0 equals death. QALY equals survival in life-years multiplied by utility weight. No studies that measured utility scores directly for women undergoing RRSO were identified. A Dutch study found no measurable impact on generic quality-of-life in high-risk women undergoing RRSO (39). Therefore, we did not include a utility decrement for RRSO in our analysis. Havrilesky (40) reported detailed utility estimates related to various health states following ovarian cancer treatment using visual analogue scale and time-trade-off (TTO) methods. As visual scales for comparing health state preferences are subject to inherent
Table 1. Probabilities of different pathways in the model*

<table>
<thead>
<tr>
<th>Probability</th>
<th>Value (95% CI)</th>
<th>Description</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>0.0245 (0.0131 to 0.0416)</td>
<td>Population prevalence of BRCA FM</td>
<td>GCaPPS</td>
</tr>
<tr>
<td>P2</td>
<td>0.52 (0.39 to 0.67)</td>
<td>Probability that carrier will undergo RRM</td>
<td>Evans (71)</td>
</tr>
<tr>
<td>P3</td>
<td>0.96 (0.8 to 0.96)</td>
<td>Reduction in risk of ovarian cancer from RRSO</td>
<td>Finch (20), Rebbeck (21)</td>
</tr>
<tr>
<td>P4</td>
<td>0.2987 (0.2485 to 0.3539)</td>
<td>Probability that carrier without RRSO will get ovarian cancer</td>
<td>Chen (61)</td>
</tr>
<tr>
<td>P5</td>
<td>0.0185 (0.0005 to 0.0989)</td>
<td>Probability that a noncarrier will get ovarian cancer</td>
<td>CRUK (84)</td>
</tr>
<tr>
<td>P6</td>
<td>0.1238 (0.1043 to 0.1454)</td>
<td>Probability of having a positive FH</td>
<td>GCaPPS</td>
</tr>
<tr>
<td>P7</td>
<td>0.0938 (0.0637 to 0.1763)</td>
<td>BRCA prevalence in FH positive individuals</td>
<td>GCaPPS</td>
</tr>
<tr>
<td>P8</td>
<td>0.0203 (0.0114 to 0.0332)</td>
<td>BRCA prevalence in FH negative individuals</td>
<td>GCaPPS</td>
</tr>
<tr>
<td>P9</td>
<td>0.91 (0.62 to 0.98)</td>
<td>Reduction in breast cancer risk from RRM without RRSO</td>
<td>Rebbeck (22)</td>
</tr>
<tr>
<td>P10</td>
<td>0.53 (0.44 to 0.62)</td>
<td>Probability that carrier without RRM will get breast cancer</td>
<td>Chen (61)</td>
</tr>
<tr>
<td>P11</td>
<td>0.13 (0.11 to 0.14)</td>
<td>Probability that a noncarrier will get breast cancer with screening</td>
<td>CRUK (46), ONS (85)</td>
</tr>
<tr>
<td>P12</td>
<td>0.55 (0.30 to 0.75)</td>
<td>Probability that carrier will follow-up with RRSO</td>
<td>Manchanda (62)</td>
</tr>
<tr>
<td>P13</td>
<td>0.49 (0.37 to 0.65)</td>
<td>Reduction in risk of breast cancer from RRSO alone</td>
<td>Rebbeck (21)</td>
</tr>
<tr>
<td>P14</td>
<td>0.95 (0.78 to 0.99)</td>
<td>Reduction in risk of breast cancer from RRM with RRSO</td>
<td>Rebbeck (22)</td>
</tr>
</tbody>
</table>

* CI = confidence interval; FH = family history; FM = founder mutations; GCaPPS = Genetic Cancer Prediction through Population Screening study; RRSO = risk-reducing salpingo-oophorectomy; RRM = risk-reducing mastectomy. P1: The probability of carrying a BRCA FM in the AJ population (p1 = 0.0245) is taken from the GCaPPS study, as it provides UK-based data and is consistent with reports from other countries (2, 86). P2: The probability that BRCA1/2 carrier will undergo RRM is taken from an analysis of UK BRCA1/2 carriers by Evans et al. 2009. A composite uptake rate (p2 = 0.52) for BRCA1 (60% RRM rate) and BRCA2 (43% RRM rate) carriers weighted for the relative prevalence of BRCA1 and BRCA2 FM found in the London AJ population was computed (71). P3: The reduction in ovarian cancer risk obtained from RRSO (p3 = 0.96) is taken from previous studies, which report a 4% residual risk of primary peritoneal cancer following RRSO (20). P4: The range of ovarian cancer risks has been reported for BRCA carriers, with higher penetrance estimates found in carriers ascertained from high-risk families with multiple cancer cases (87). Our analysis uses the ovarian penetrance figures (40% for BRCA1, 18% for BRCA2) from a meta-analysis, corrected for ascertainment (61). P5: The probability of carrying a BRCA FM in a low-risk population (p5 = 0.0185) is taken from Cancer Research UK (84). P6: The probability of having a strong FH of cancer fulfilling the current clinical criteria (FH-positive) is obtained from the population-based GCaPPS study (p6 = 0.1238 or 128/1034). P7, P8: The BRCA FH prevalence in FH-positive (p7 = 0.0975%) and FH-negative (p8 = 0.0203%) individuals is also obtained from the GCaPPS study in which 12/128 BRCA carriers detected were FH-positive and 15/740 were FH-negative. P9: Reduction in breast cancer risk from RRM in BRCA carriers not undergoing RRSO is taken from the PROSE study data by Rebbeck et al., JCO 2004 (22). P10: The breast cancer penetrance for BRCA carriers (57% for BRCA1 and 49% for BRCA2) is taken from a meta-analysis, corrected for ascertainment (61). To simplify the analysis, we have used a composite risk for BRCA1 and BRCA2 carriers (p10 = 0.53) weighted for the relative prevalence of BRCA1 and BRCA2 FM found in the London AJ population. P11: The probability of undergoing RRSO is taken from the PROSE study data by Rebbeck et al., JCO 2004 (22). P12: The probability that a noncarrier will get breast cancer with screening is obtained from Cancer Research UK (84). P13: The reduction in breast cancer risk from RRSO alone was taken from a meta-analysis by Rebbeck et al. (21). P14: The reduction in breast cancer risk from RRM in BRCA carriers undergoing RRSO is taken from the PROSE study data by Rebbeck et al., JCO 2004 (22).

Biases and are generally less accurate (41), we utilized the TTO scores. We assumed 70% of women present with ovarian cancer at advanced stages (42,43), with a lower utility score for a new diagnosis at 0.55 (SD = 0.29), while the remaining presenting at early stages have a higher utility score of 0.81 (SD = 0.26). The end-stage-of-life utility score, where ovarian cancer patients did not survive the next year, was 0.16 (SD = 0.25). Of those that survived initial chemotherapy, the chance of recurrence with early disease was 10.5% annually (44), and with advanced disease this would be 20.6% (42). For women with recurrent disease, the mean utility value was 0.5 (range = 0.4–0.61), and for women in remission the utility value was 0.83 (SD = 0.25) (40).

Of general population breast cancer, 10% is invasive/DCIS, 90% is invasive, 95% of invasive cancer is early and locally advanced (41% = stage 1, 45% = stage 2, 9% = stage 3) (45–48), and 5% is advanced (stage 4) (45–47). In BRCA carriers, 20% of cancers were DCIS and 80% invasive (61% = stage 1) (18,49). Utility weights for breast cancer were assumed as follows: advanced breast cancer was 0.65, early or locally advanced breast cancer was 0.71, remission was 0.81, recurrence was 0.45; these were obtained from NICE guidelines (50,51). For those who survived initial chemotherapy, the chance of breast cancer recurrence/progression with early or locally advanced disease was 35% (47), and for recurrence with advanced disease it was 66% (52).

Statistical Analysis

For each branch of the decision model, the probability of being in each branch was calculated by multiplying together the path probabilities. The total costs and effects in terms of life-years and QALYs were then estimated by weighting the values for each...
branch by the probability of being in each branch. The incremental cost-effectiveness ratio (ICER) was estimated by dividing the difference in cost by the difference in effect. ICER = (Cost A–Cost B)/(Effect A–Effect B). By comparing this ICER with the cost-effectiveness threshold used by NICE (£20000–£30000/QALY) (53), it was possible to determine whether or not population screening for all women was cost-effective compared with FH-based testing. To explore uncertainty in the results and robustness of the model, a one-way sensitivity analysis was undertaken by varying each parameter in the model and then rerunning the model to assess the impact on overall results. Probabilities and utility scores were varied according to their 95% confidence intervals/range, where available, or by +/-10%, and costs were varied by +/-30%. In addition to the one-way sensitivity results, a probabilistic sensitivity analysis (PSA) was undertaken as recommended by NICE methods guidance (25,54). Any variation in model parameters/variables is likely to occur in parallel rather than independently of each other. In the PSA all variables are varied simultaneously across their distributions to further explore model uncertainty. We assigned costs a gamma distribution, probabilities a beta distribution, and utilities a log-normal distribution as suggested in the literature (55). The results of 1000 simulations were plotted on a cost-effectiveness acceptability curve showing the proportion of simulations that indicated that the model is cost saving. FH = family history; neg = negative; pos = positive; RRSO = risk-reducing salpingo-oophorectomy; RRM = risk-reducing mastectomy.

2) women opting for genetic testing at age 50 years (average age of menopause) with a median age for RRSO and RRM at 54 years (just below the weighted average age of ovarian cancer onset in BRCA1/BRCA2 carriers).

Results

The discounted and undiscounted lifetime costs, life-years, and QALYs for each branch in the decision model are given in Table 3. Overall, a population-screening approach saved more life-years (0.090) and QALYs (0.101) than an FH-based approach. This difference equated to 33 days’ gain in life expectancy for AJ women using a population-screening strategy compared with an FH-based one. Discounted results show a smaller overall gain in life-years and QALYs and overall cost difference, as discounting adjusts costs and outcomes that occur in the future and the cost savings generated through prevention of future ovarian cancer cases is valued less. The baseline discounted ICER was -£2079 per QALY, indicating that population-based screening not only saves more QALYs but is also cost saving and is highly cost-effective in AJ women. This is well below the NICE threshold of £20000–£30000/QALY. Population-based screening also lowered ovarian cancer incidence by 0.34% (from 2.49% to 2.15%) and lowered breast cancer incidence by 0.62% (from 13.31% to 12.69%). Assuming that 71% of the estimated 114,000 AJ women in the UK (26,27) undergo testing, the overall impact of a population-based strategy is a reduction in ovarian cancer and breast cancer by 276 and 508 cases, respectively, at a discounted cost savings of
£3.7 million. Should the entire population undergo testing, the number of cancers potentially prevented would increase to 388 for ovarian and 715 for breast cancers at a discounted cost saving of £5.2 million.

The results of the one-way sensitivity analysis (Figures 2,3) indicate that the upper/lower utility values, costs, penetrance estimates, and rate of uptake of preventive/risk-reducing surgery have little influence on the overall results, and the model is cost saving at both upper and lower limits of these variables. However, the model is highly sensitive to the overall BRCA prevalence and BRCA prevalence in FH-negative women (Figure 2). At the lower limits of overall BRCA prevalence and BRCA prevalence in FH-positive individuals, the intervention was still just cost saving at -£183/QALY and -£631/QALY, respectively. At the lowest value for BRCA prevalence in FH-negative women, the ICER equals £3877 per QALY, well under the NICE threshold of £20000 to £30000 per QALY, indicating that population screening was still cost-effective, but no longer cost saving. At the highest BRCA prevalence rates in FH-positive and FH-negative women, the intervention was both more effective and cost saving.

The probabilistic sensitivity analysis results (Figure 4) shows that at a threshold of £20000 94% of simulations indicate that population screening in AJ women is a cost-effective intervention compared with current NHS policy. A scenario incorporating breast cancer prophylaxis with tamoxifen (premenopausal)/raloxifene (postmenopausal) in BRCA carriers, as recently recommended by NICE (19), achieved a greater cost savings per QALY of -£2472 for population-based screening compared with FH-based testing. A further scenario where unaffected women age 50 years were screened for BRCA mutations (with a median age for RRSO and RRM = 54 years), also achieved a higher cost savings per QALY of -£2946.

**Discussion**

According to NICE, a cost-effectiveness analysis comparing the relative health outcomes and costs of interventions is the preferred form of economic evaluation, and QALY is the most suitable determinant of health benefit, reflecting both mortality and health-related quality-of-life effects (25). Value-based judgments are used to assign an appropriate price for health outcomes. This analysis focused on whether the cost differential between different interventions/strategies is worthwhile in terms of changes in health outcomes. Our decision analysis model addressed the topical issue of cost-effectiveness of a new population-based BRCA testing strategy in AJ women, made possible by identification of AJ founder mutations and advances in the efficiency/cost of technology for mutation detection. Our finding that a population screening program implemented in UK AJ women older than age 30 years will be cost saving compared with the current FH-based one has important implications for clinical care, population/public health, and for health care providers and commissioners. There is potential within the UK for reduction of the number of ovarian cancers by 276

![Figure 3. Deterministic sensitivity analysis for model costs and utilities. One-way sensitivity analysis for all model costs and utility-score parameters in terms of the incremental cost-effectiveness ratio (ICER) of population-based screening compared with a family history (FH)-based approach for BRCA testing. X-axis: ICER: cost (£s) per quality-adjusted life-year (QALY) (discounted). Y-axis: cost and utility-score parameters in the model. The model is run at both lower and upper values/limits of the cost and utility-score parameters given in Table 2. “High value” represents outcomes for upper limit, and “Low value” represents outcomes for lower limit of these parameters. Outcomes to the left of the midline “0” value on the X-axis indicate that the model is cost saving. This analysis suggests that variation in costs and utility scores do not statistically significantly affect model outcomes. BC = breast cancer; FH = family history; neg = negative; OC = ovarian cancer; pos = positive; RRSO = risk-reducing salpingo-oophorectomy; RRM = risk-reducing mastectomy.](image-url)
Radiotherapy and chemotherapy: Invasive breast cancers that are not low risk (NICE guidelines [25,30-32], ER-positive invasive breast cancers receive Tamoxifen 20 mg/day (premenopausal)/Aranzolone 1 mg/day (postmenopausal) for five years: costs from the BNF [91]. Rates are adjusted for BRCA carriers, ER positivity, and menopause status. Biphosphonate costs: 74% patients with advanced breast cancer will develop bone metastases, and 65% patients with bone metastases are offered bisphosphonates [47,109,110]. As per NICE guidelines, costs (from BNF [91]) assume that 50% patients receive oral clodronate and ibandronic acid, and 50% receive intravenous zoledronic acid or pamidronate [47]. Cost of Trastuzumab: for HER2-positive patients, given at three-week intervals for one year or until disease recurrence as per NICE guidelines. Costs obtained from NICE costing report [47]. 35% of early/locally advanced breast cancer progress to advanced breast cancer (NICE guidelines [47]). Recurrence rate for early/locally advanced breast cancer (from the US National Surgical Adjuvant Breast and Bowel Project [NSABP]): 15.9% for node-positive (111) and 11% for node-negative (112) breast cancer: composite recurrence rate = 12.6% (weighted for 31% node-positive and 69% node-negative disease). Recurrence rate for advanced/metastatic breast cancer is 66% (24% relapse free five year survival) [52]. Follow-up costs: includes annual mammograms and six monthly consultations. MRI scan for all four cancers. Costs include a progression rate of 35% from early and locally advanced to advanced disease [47], and 66% relapse rate for advanced disease [52]. Costs for terminal care for breast cancer were derived from end-of-life costs for cancer patients based on a report from the National Audit Office, UK [93]. In line with NICE recommendations, future healthcare costs not associated with breast cancer were not considered [25]. Chemoprevention (sensitivity analysis): Tamoxifen/Raloxifene for five years [51,52], from BNF [91].

†For more detailed explanation, see Supplementary Table 2 (available online).
Table 3. Model outcomes for costs, life-years, and quality-adjusted life-years (QALYs), undiscounted and discounted

<table>
<thead>
<tr>
<th>Population screening</th>
<th>Probability</th>
<th>Cost, £</th>
<th>Life-years</th>
<th>QALYs</th>
<th>Cost, £</th>
<th>Life-years</th>
<th>QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. PS, carrier, RRM, RRSO, no OC/BC</td>
<td>0.0068</td>
<td>5197</td>
<td>53.00</td>
<td>53.00</td>
<td>3819</td>
<td>23.40</td>
<td>23.3888</td>
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<tr>
<td>B. PS, carrier, RRM, RRSO, OC</td>
<td>0.0001</td>
<td>30 343</td>
<td>38.20</td>
<td>37.22</td>
<td>13550</td>
<td>19.75</td>
<td>19.39</td>
</tr>
<tr>
<td>C. PS, carrier, RRM, RRSO, BC</td>
<td>0.0002</td>
<td>27 936</td>
<td>46.92</td>
<td>45.63</td>
<td>28033</td>
<td>21.48</td>
<td>20.74</td>
</tr>
<tr>
<td>D. PS, carrier, RRM, no RRSO, no OC/BC</td>
<td>0.0038</td>
<td>2976</td>
<td>53.00</td>
<td>53.00</td>
<td>2766</td>
<td>23.40</td>
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<tr>
<td>E. PS, carrier, RRM, no RRSO, OC</td>
<td>0.0017</td>
<td>28 121</td>
<td>38.20</td>
<td>37.22</td>
<td>12497</td>
<td>19.75</td>
<td>19.39</td>
</tr>
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<td>F. PS, carrier, RRM, no RRSO, BC</td>
<td>0.0003</td>
<td>25 715</td>
<td>46.92</td>
<td>45.63</td>
<td>26960</td>
<td>21.48</td>
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Family history screening

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* Cancer incidence. BC = breast cancer; FH = family history; neg = negative; OC = ovarian cancer; pos = positive; PS = population screening; QALY = quality-adjusted life-year; RRSO = risk-reducing salpingo-oophorectomy; RRM = risk-reducing mastectomy.
† Reduction in total number of cancer cases.

and breast cancers by 508, combined with overall cost savings of £3.7 million. Should the entire relevant UK population undergo testing, the number of cancers potentially prevented would increase to 388 for ovarian and 715 for breast cancer at a discounted cost savings of £5.2 million. This compares favorably with a number of interventions routinely used in clinical practice, which, while saving lives, cost more. For instance, the ICER for breast screening in BRCA1/BRCA2 carriers age 35 to 49 years recommended by NICE (56) is £11 700 (MRI alone) or £15 300 (MRI+mammography) per case of cancer detected (57). The ICER for paclitaxel and cisplatin for primary treatment of ovarian cancer ranges between £6600 and £22 000 per life-year gained (58, 59).

This is the first report comparing cost-effectiveness of population screening for founder mutations of BRCA1/2 with the current standard of care. Our analysis incorporates impact on both breast and ovarian cancer risk and fulfills various requirements suggested by NICE for health-economic decision-making. The "time horizon" in our analysis is long enough to reflect important differences in costs and outcomes (25). We use current best practice as a comparator, QALYs to measure health outcomes, a 3.5% discount rate on costs and health outcomes, and, as far as possible, directly obtained population-based data for parameters in the analysis (25). This is the first model to incorporate BRCA prevalence in FH-negative individuals, and probabilities used in the model are consistent with other
reports in the literature (2,60). A comparison of population-screening for BRCA carriers vs no screening reported an ICER of $8300 per QALY (17). This higher value compared with the cost savings in our study could be attributable to our lower costs of testing, higher health care costs in the United States compared with the UK, and the beneficial impact of breast cancer prevention found in our study but not evaluated by the earlier study (17). Another advantage of our model is that it also includes genetic counseling costs, which would be a key component of any population-based testing strategy. This approach facilitates reflection of the positive and negative consequences of genetic testing and permits participants to make informed decisions based on their own values and opinions. In order to minimize overestimating benefits of population-based screening, we have been conservative in our use of ovarian and breast cancer penetrance estimates (corrected for ascertainment) (61), as well as our costs for ovarian and breast cancer diagnosis and treatment, by including a minimal subset of baseline costs. We did not include all costs for additional investigations, treatment of recurrence, or management of complications.

The deterministic sensitivity analysis permitted scrutiny of model outcomes and identification of variables that exert the most influence (Figures 2 and 3). The 95% confidence limits for probabilities explored in our sensitivity analysis were quite wide, adding to the strength of the results. The lack of statistically significant effect on outcome despite 30% variation in costs indicates that costs of counseling, treatment, and prevention are less important in influencing the overall results. BRCA prevalence rates (P1, P8) emerged as the key variables of influence, given the higher model sensitivity to uncertainties around these values (Figure 2). That the model remains largely cost saving despite probabilities varying widely is reassuring. Even at low prevalence rates in FH-positive or FH-negative individuals, population testing remained cost-effective compared with the NICE threshold of £20000 to £30000 per QALY (53). Though we used an RRSO risk-reduction estimate (0.96) based on the residual risk of PPC (20), a lower rate of 0.8 (21) assessed in the sensitivity analysis showed it was still cost saving. RRSO rates vary with time, menopausal status, age, and parity (62). It is encouraging that even at low (0.3) RRSO rates, the model remains cost saving (Figure 2). The PSA undertaken adds to the robustness of our results and has been recommended by decision-making bodies (25). It permits simultaneous variation in probabilities of all parameters to fully characterize uncertainties in the model and its effect on overall results. That 94% of simulations on PSA were cost-effective reconfirms the health-economic benefit of a population-based approach to genetic testing.

Our model is limited by a number of assumptions. It does not incorporate any potential reduction in QALY following RRSO. Although RRSO is associated with worse menopausal symptoms and sexual function compared with women undergoing screening, no difference in generic quality-of-life has been reported (39,63,64). RRSO has also been linked with a higher risk of cardiovascular disease (65,66) and osteoporosis. We felt that these downsides in premenopausal women may be balanced by the decrease in vasomotor symptoms, cardiovascular sequelae, and improved sexual function and osteo-protection seen with hormone replacement therapy (HRT) (63,65,67–69), as well as the reduction in cancer worry, perceived risk, and high overall satisfaction observed following RRSO (39,63). RRSO also halves the risk of subsequent breast cancer in premenopausal women (21), and available evidence suggests that HRT does not alter the statistically significant benefit of reduction in breast cancer risk obtained from bilateral oophorectomy (70).

Of BRCA carriers, 21% to 67% undergo risk-reducing mastectomy (71–73). Addition of risk-reducing mastectomy or screening to RRSO further increases life expectancy in BRCA carriers (74). Our model incorporates the impact of breast screening already prevalent in the UK and includes the benefits of reduction in breast cancer risk obtained from RRSO (21) and risk-reducing mastectomy (RRM) (22). Our analysis does not incorporate any potential reduction in QALY following RRM. Although a negative impact on sexual pleasure and body image has been reported, no difference over time in sexual habit, discomfort, or activity...
was documented (75). Lack of adverse effects on anxiety, depression, and health-related quality-of-life over time has also been reported (18,75,76). Additionally, any negative effects of RRM could be balanced by findings of significant decreases in anxiety scores, improved social activity (75), reports of a majority of women finding RRM results to be consistent with their expectations, and high satisfaction with overall cosmetic results (76–79).

Although it can be hypothesized that FH-positive women may be more likely to adapt to their increased risk while FH-negative women have less of an opportunity to consider/adapt to these issues before being tested, we did not find FH to statistically significantly affect quality-of-life outcomes in our GCaPPS trial. Not all of those undergoing genetic counseling will opt for genetic testing, and a reduced genetic testing uptake rate is built into the model costs. A total of 1034 (71%) of 1450 people who made a genetic counseling appointment in the GCaPPS study underwent BRCA testing. This equals 1034 (89%) of the 1168 who attended pretest counseling. FH did not statistically significantly influence uptake of testing in our population-based trial; hence, uptake using either FH or population approaches in our decision model is assumed to be similar (71%). This estimate lies well within the range of genetic testing rates (varying from 66%–90%) (80–83), reported by previous studies of varying ascertainment and sizes.

The marriage rate in the Jewish community is likely to lead to a fall in BRCA founder mutation prevalence. Twenty-five percent of Jewish marriages in the UK and 44% in the United States are to non-Jews, although only 50% of the population is married. Hence, overall, the impact of this is unlikely to affect more than 25% of the population. Assuming a BRCA prevalence of 2.5% for 75%, and 1% for 25% of the population, the overall population BRCA prevalence will be about 2.1%. Even if BRCA prevalence were 1% for 50% of the population, the overall population prevalence would be about 1.75%. These extremes are well within the 95% confidence intervals accounted for in our sensitivity analysis, which shows the model to be cost-effective.

Implementation of any national screening program has many challenges and raises important issues of logistics and quality control. It also requires raising public (and health professional) awareness/education, community engagement, and information dissemination via media campaigns, which have an added cost. In the UK, screening programs are centrally coordinated by the national screening committee with fail-safe procedures and involve close coordination with GP/primary care and public health physicians. In addition, there is need for clearly defined downstream secondary and tertiary care pathways, developed in close coordination with clinical genetics teams, breast surgeons, gynecologists, and others responsible for the management of women found to be at high risk. While these pathways exist for high-risk women, they would need to be expanded prior to program implementation. It would not be sensible or feasible for all women to undergo pretest counseling in tertiary high-risk cancer genetics clinics within a hospital setting, so a community-based approach would need to be explored. We have demonstrated that successful recruitment to such a population-based program for pretest counseling and BRCA testing outside a hospital setting is possible using a community- or high street–based model. More efficient, acceptable, and cost-effective ways of delivering information on genetic risk will be needed for any population-based testing program to become a reality, and this area should be the focus of further research.

Health-economic assessments are critical for determining the appropriateness of resource allocation for cost-intensive population-based interventions. Rising health care costs and the ever-increasing price of new ovarian/breast cancer treatments and drug therapies in a challenging economic environment further magnify the importance of newer cost-effective preventive strategies. An important advantage of population screening is the ability to identify BRCA carriers without a strong FH of cancer undetectable by an FH-based approach. This translates to 2232 additional UK AJ women (population prevalence = 0.23%, 95% CI = 1.14% to 3.32%) who may benefit from access to screening/preventive options. The lack of statistically significant difference in short-term outcomes of anxiety, depression, quality-of-life, health anxiety, and overall impact of genetic testing between FH and population-based approaches reconfirms that population-based genetic testing in the majority of Jewish people does not harm quality-of-life or psychological well-being, or lead to excessive health concerns (11).

The high cost-effectiveness of population-based testing in AJ women demonstrated in this analysis combined with the above findings should justify a change in the current paradigm, which is limited to an FH-based approach to BRCA testing in the AJ population. We conclude that introduction of systematic population testing for AJ BRCA1/2 founder mutations could save both lives and financial resources. Finally, we emphasise that the results from our analysis are related to population-based BRCA testing in AJ women and cannot be directly extrapolated to non-AJ populations with lower prevalence rates for BRCA1/2 mutations. Nevertheless, as the cost of testing falls and the acceptance/understanding of this type of health intervention evolves in our societies, it is likely to become an increasingly important area for research and evaluation.

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Notes

Ethics approval and trial registration: The Genetic Cancer Prediction through Population Screening (GCaPPs) study received full ethics approval from the Institute of Child Health/Great Ormond Street Hospital Research Ethics Committee on June 8, 2008 (Research Ethics Committee [REC] Reference number 08/H0713/44). The study was registered with the International Standard Randomized Controlled Trial Number Register - ISRCTN 73383115 (http://www.controlled-trials.com/ISRCTN73383115). Contribution to authorship: IJ conceived the GCaPPs study. IJ and RM developed concept and design of the GCaPPs study. RM, RL, IJ, and UM were responsible for literature search and design of the HE study. RM and RL developed the model. RM, RL, AM, MR, and MB were involved in the health-economic and statistical analysis. RM, KL, and MB were involved in data collection and analysis. RM and RL prepared the tables and figures. RM, IJ, UM, KL, JW, SG, LS, NB, RD, AK, HD, YW, CC, IT, AMG, and UB were involved in running the GCaPPs study. YW did the genetic testing. RT and CJ were collaborators and helped with data collection from genetic laboratories. RM and RL prepared the first draft of the manuscript. All authors critically contributed to and revised the manuscript and approved the final version.

Disclaimers/conflict of interest statement: IJ and UM have a financial interest in Abcodia Ltd., a company formed to develop academic and commercial development of biomarkers for screening and risk prediction. IJ is a member of the board of Abcodia Ltd. and a Director of Women’s Health Specialists Ltd. IJ holds an NIHR Senior Investigator Award. The other authors declare no conflict of interest.
Role of Funding Source: The study was funded by The Eve Appeal charity. The funding body (The Eve Appeal charity) had no role in the study design, data collection, analysis, or interpretation, the writing of the report, nor decision to submit for publication. The research team was independent of funders. The study was supported by researchers at the National Institute for Health Research, University College London Hospitals Biomedical Research Centre.

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